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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/629,351	07/29/2003	Claes Gustafsson	MXGNP004X1/0311.310US	6357

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MAXYGEN, INC.
INTELLECTUAL PROPERTY DEPARTMENT
515 GALVESTON DRIVE
REDWOOD CITY, CA 94063

EXAMINER	
SKIBINSKY, ANNA	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/629,351	GUSTAFSSON ET AL.	
	Examiner	Art Unit	
	Anna Skibinsky	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-81 and 101-119* is/are pending in the application.

4a) Of the above claim(s) *101-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *76-81 and 101-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/24/2007 has been entered.

Election Restriction

Applicants elected Group XI (original claims 76-81) in the restriction requirement filed 3/28/2006, drawn to a method and computer program produce for identifying nucleotides for variation in nucleic acids encoding protein and from the data developing a sequence activity **model that predicts activity** as a function of nucleotide types and corresponding position in the nucleotide sequence.

Newly presented claims 109-119, are drawn to developing a sequence activity **model that predicts the quantity of protein expressed** as a function of nucleotide types and corresponding position in the nucleotide sequence. These claims are therefore patentably distinct because the method of claims 109-119 is directed to developing a model that has a different mode of operation and effect, wherein the elected model is one that predicts activity of the protein and the non-elected claims 109-119 are to a model that predicts quantity of protein express.

Thus, newly presented claims 109-119 are not drawn to the originally elected invention and are therefore withdrawn from examination.

Response to Applicants

Amendments to claims 76 and 79 and new claims 101-108 are acknowledged. Claims 76-81 and 101-108 are under examination.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 76-81 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 7-9 and 14 of copending Application No.11/706034 in view of Hellberg et al.. Although the conflicting claims are not identical, they are not patentably distinct from each because it would be obvious to use non-linear terms; e.g. as taught by Hellberg et al. in the sequence activity model in claims 1 and 8 of '034.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 101

The rejection of claims 79-81 under 35 U.S.C. 101 is withdrawn in light of amendments filed 5/24/2007.

Claims 79-81 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 79-81 are drawn to a computer program product comprising a program that carries out a process for identifying nucleotides for variation. The process carried out by the computer program product is a non-statutory process. The process according the claimed method involves the application of algorithms and computations and, therefore, involves the application of a judicial exception. Regarding inventions involving the application of a judicial exception, said application must be a practical application of the judicial exception that includes either a step of a physical transformation, or produces a useful, concrete, and tangible result (State Street Bank & Trust Co. v. Signature Financial Group Inc. CAFC 47 USPQ2d 1596 (1998), AT&T Corp. v. Excel Communications Inc. (CAFC 50 USPQ2d 1447 (1999)). In the instant claims, there is no step of physical transformation, thus the instant claims must recite a practical application; i.e. recite a useful, concrete, and tangible result. See MPEP 2106, in particular, Section IV, for an explanation of a concrete, tangible and useful result.

Claims 79-81 do not recite a tangible result. A tangible result requires that the claim must set forth a practical application to produce a real-world result. Examples of a "real-world result" include a physical transformation of matter, or a step of communicating the result in a TANGIBLE format to a user; e.g. by outputting or displaying the result of the method. Applicant is reminded that any amendment must be fully supported and enabled by the originally filed description.

As the claims do not recite a physical transformation of matter OR a concrete, tangible and useful result, they are not directed to statutory subject matter.

Reply to Arguments

Applicant's arguments filed 5/24/2007 have been fully considered but they are not persuasive.

Applicants argue (Remarks, page 7) that claim 79 drawn to a computer program has been amended to recite that a result can be generated in a computer.

In response, this amendment is not sufficient for the claim to become statutory because the process carried out by the program is still non-statutory. Generating a result within a computer is not a tangible, "real world result". Thus, as a consequence of the process being non-statutory, the computer program product of claim 79 is also not statutory.

Claim Rejections - 35 USC § 102

The rejection of claim(s) 76-81 over Wang et al. in the Office Action filed 11/29/2006 is withdrawn in view of Applicant's Remarks/Amendments filed 5/24/2007.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 76-81 and 101-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellberg et al. (Journal of Medicinal Chemistry, vol. 30 (1987) pages 1126-1135) in view of Voigt et al. (Journal of Cellular Biochemistry Supplement, vol. 37 (2001) pages 58-63).

1. The instant claims recite a method for identifying amino acid residues for variation in a protein variant library. The identifying entails the characterization of a training set of protein variant sequences and determining which amino acids in the sequence have the greatest impact on the activity of the sequence.

1. Claim 76(a) recites receiving data characterizing a training set of a protein variant library of systematically varied sequences where the data comprises activity and amino acid sequence for each protein variant in the training set.

2. Hellberg et al. teach the measurement of various properties of amino acids in a peptide (page 1128, col. 1, lines 6-4 from bottom) and data from compounds with known biological activity, a training set, used to construct a model (page 1130, col. 1, lines 3-7 from bottom).

3. Claim 76 (b) recites developing a sequence activity model that predicts activity as a function of amino acid residue type and position in the sequence.

4. Hellberg et al. teach a model constructed from the training set that is used to predict structures that improve biological activity (page 1130, col. 1, lines 1-7 from bottom). The chemical structure is quantified by varying amino acids at certain positions. The structure activity relationship is analyzed with regard to introduction or deletion of features at various positions in the peptides (page 1127, col. 2, lines 6-10 from bottom; page 1128, col. 1, lines 37-45; and col. 2, lines 1-19).

2. Claim 76, step (c) recites ranking positions in a nucleotide sequence or types at specific positions in order of impact on the desired activity.

3. Hellberg et al. teach using the model to quantify peptide analogues where each varied amino acid is described by variables (page1128, col. 2, section "II. Peptide Description"). A test matrix is taught where the amino acid with the highest absolute z values are chose to be included in a test series (page 1129, col. 2, ¶ 7 and Table V) and shows a test series of 16 peptides with four amino acid positions that were varied.

4. Claim 76, step (d) recites using the ranking to identify one or more nucleotides, in the reference nucleotide sequence that are to be varied or fixed in order to impact the desired activity.

5. Hellberg et al. teach varying positions 2 and 4 in Pepstatin Analogues (Example III, page 1133, col. 1) wherein the calculated activity of seven analogues are plotted as function of activity in Figure 3.

6. Claim 76(e) recites generating on or more of the protein variants encoded by the reference nucleotide sequence with the identified nucleotides that are varied or fixed.

7. Hellberg et al. teach generating the analogues having the identified amino acid residues varied in order to impact desired activity, as shown in Figure 3. Furthermore, Hellberg et al. teach the design a series of analogues based on the analysis done with the activity model (page 1128, col. 1., lines 45-49; and page 1129, col. 2, section "Design Example").

5. As in claim 77, Hellberg et al. further teach that their model is not limited to amino acid sequences but that a design for only coded amino acids, a set of codon sequences (i.e. nucleotides in DNA) can be constructed that corresponds to a set of designed peptide fragments (page 1135, col. 2, ¶2).

6. Hellberg et al. teach performing steps (a)-(c) using activity and sequence data from protein variants, page 1135, col 2, ¶ 2), as in claim 107.

8. Hellberg et al. teach a computational sequence activity model that predicts activity as a result of varied amino acid sequences and the synthesis of proteins based on the predictions of the model. Hellberg et al. teach using data which comprises activity and an amino acid sequence and does not teach using the method with nucleotide sequences to generate protein variants, as required in claim 76.

9. Hellberg et al do not teach a library of protein mutants generated from nucleic acid sequences and using directed evolution methods such as gene synthesis, mutagenesis, and recombination-based screening where nucleotide sequences are used to generate protein libraries based on the prediction of the activity model. Voigt et al. however does teach a mutant library and using mutations in genes to create a protein variant library wherein directed evolution methods such as gene synthesis,

mutagenesis, and recombination-based methods are used in relation to computational algorithms.

10. Claims 76 and 79-81 recite a computational algorithm and computer program product comprising a machines readable medium with program instructions to carryout the method of the claimed invention.

11. Voigt et al. teach computational methods (i.e. carried out with a computer) for the optimization of mutant libraries.

12. Voigt et al. teach creating protein libraries from directed evolution and mutation of genes where the resulting mutant libraries are screened for improvements in properties (i.e. activity) (Abstract and page 58, col. 1, ¶ 1-2), as in claim 78.

13. Voigt et al. teach generating diversity by directed evolution applied randomly to the gene in protein engineering and resulting in a library (page 58, col. 1, lines 1-15), as in claims 101 and 102.

14. Voigt et al. teach creating diversity through "mutagenesis" to create a resulting library of proteins (page 58, col. 1, lines 1-15 and section "Targeted Mutagenesis Algorithms"), as required by claim 103 reciting performing mutagenesis using polynucleotide sequences to generate a protein variant library.

15. Voigt et al. teach exchanging genetic information from parent genes to generate a library of recombinant mutants (page 58, col. 1, lines 1-15, page 61, col. 1, lines 14-22, and section "Targeted Mutagenesis Algorithms" and "Recombination Strategies"), and using screening techniques such as the algorithm discussed to identify the genes

encoding stable proteins, as required by claim 104 reciting using a recombination-based diversity generation mechanism.

16. Voight et al. also teach screening the resulting library for improvements and interesting properties as a result of protein engineering (page 58, col. 1, lines 1-6), as required by claim 105.

17. Voigt et al. teach simulations of the amino acids to understand interactions between them (page 58, col. 2, lines 9-19) wherein the model describing the properties of small libraries of mutants, generated by PCR (page 59, col. 1, lines 1-14), as in claim 106.

18. Voigt et al. teach a slow mutation rate where the (page 59, col. 1, lines 15-29 and Figure 1), as in claim 108.

19. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have implemented the sequence activity model of Hellberg et al. to generate a protein variant library with the directed evolution methods as taught by Voigt et al. One of ordinary skill in the art would have been motivated to use genes and directed evolutionary methods of Voigt et al. because Voigt teach the effectiveness of generating maximum fitness as a result of diversity (Voigt, page 59, col. 1, ¶ 2). One of skill in the art would have had a reasonable expectation of success at utilizing the structure activity model of Hellberg et al. with the expression of protein sequences via gene synthesis, mutagenesis and recombination because Voigt e et al. teach that computational techniques allow for the optimization of directed evolution (Voigt, page 58, col. 2, lines 8).

Response to Arguments

Applicant's arguments filed 5/24/2007 have been fully considered but they are not persuasive.

Applicants argue that Wang does not teach a developing a sequence activity model wherein the data used to develop the model comprises activity and a nucleotide sequence for each protein variant in the training set (Remarks, pages 7-8).

In response, Hellberg et al. do teach developing a sequence activity model from a training set of sequences while Voigt et al. teach a protein variant library developed from nucleic acid sequence, as argued above in the new rejection of claim 76.

Applicants argue that Wang does not teach using the sequence activity model to rank positions in a nucleotide sequence in order of impact on desired activity (Remarks, page 9).

20. In response, Hellberg et al teach varying positions 2 and 4 in Pepstatin Analogues (Example III, page 1133, col. 1) as those being the most effective for impacting activity and wherein the calculated activity of seven analogues are plotted as function of activity in Figure 3.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anna Skibinsky whose telephone number is (571) 272-4373. The examiner can normally be reached on 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anna Skibinsky, PhD

MARJORIE A. MORAN
PRIMARY EXAMINER

Marjorie A. Moran
9/12/10